Pancreas (2)

ILOs:

After this lecture, student should be able to:

Explain the consequences of deficient insulin secretion or insulin action.

List the physiological effects of glucagon.

Enumerate factors that regulate glucagon secretion.

Describe the physiologic effects of somatostatin in the pancreas.

List the anti-insulin hormones.

Summarize the hormones that affect the plasma glucose concentration and briefly describe the action of each.

Consequences of insulin deficiency

Effect of insulin lack: Diabetes Mellitus

It produces the following abnormalities:

a. Decreased utilization of glucose by the body cells, and so **hyperglycemia.**

b. Increased mobilization of fats from adipose tissue **(lipolysis)** causing abnormal plasma lipoprotein, increased deposition of cholesterol in arterial walls, and **atherosclerosis**

c. Depletion of proteins in the tissues of the body **(catabolism).**

Pathophysiology and symptoms:

A. Effects of Hyperglycemia:

I. **Glucosuria:** because the renal threshold for glucose reabsorption is exceeded (all carriers become saturated).

II. **Polyuria:** due to osmotic dragging of water, causes dehydration (**osmotic diuresis**).

III. **Polydipsia:** dehydration stimulates hypothalamic osmoreceptors causing thirst.

IV. **Elevated HbA1c**: normally small amounts of hemoglobin A are non-enzymatically glycosylated (glucose attached to the B chain in hemoglobin molecule) to form HbA1c (N: 4-6%). It is increased in case of prolonged hyperglycemia.

V. **Polyphagia** (excessive eating): its mechanism is:

- Reduced glucose utilization by the glucostats of the satiety center in the hypothalamus decreases their activity.

A. Feeding center is released from the normal inhibitory effect of the satiety center.

B. Abnormal Fat Metabolism:

i. The uninhibited hormone-sensitive lipase enzyme in adipose tissue, causes **lipolysis** and the plasma level of **FFA** is increased.

ii. The catabolism of fatty acids by liver into **acetyl-CoA** is markedly increased leading to excess formation of acetyl-CoA. & ketone bodies --→ **Ketosis**

C. Abnormal protein metabolism: decreased intracellular glucose stimulates protein catabolism & gluconeogenesis, leads to loss of weight and lack of energy: asthenia.

Complications of Diabetes Mellitus:

A. Acute complications: includes coma

B. Chronic complications: includes (Macrovascular and Microvascular complications) increased risk for heart attack, stroke, ischemia and gangrene of the limbs

(Macrovascular complications), and end-stage kidney disease **(nephropathy), retinopathy**, blindness, and **neuropathy (Microvascular complications).**

GLUCAGON

Human glucagon is a polypeptide (29 AA) produced by the A cells of pancreatic islets and also the upper GIT.

ACTIONS OF GLUCAGON

What is the role of glucagon hormone in metabolism?

1- On carbohydrate metabolism:

It is called the **hyperglycemic** hormone. This effect is through:

a) Breakdown of liver glycogen **(glycogenolysis)**, **not** in muscle.

b) Increased of **gluconeogenesis** in the liver.

2- On protein metabolism: glucagon stimulates the enzymes required for A.A. uptake by the liver cells and their conversion into glucose by gluconeogenesis

3- On fat metabolism: - In high concentrations glucagon causes lipolysis in adipose tissues by activating adipose cell hormone-sensitive lipase. This increases fatty acids utilization for energy, which leads to **ketogenesis**. It also

inhibits triglycerides storage in liver to spare more fats to other tissues.

4- Calorigenic action: Is due to increased deamination of A.A. and increased gluconeogenesis from A.A. in the liver elevates the metabolic rate.

5- Large doses of exogenous glucagon exerts **+ve Inotropic effect** on the heart by increasing myocardial cAMP

Regulation of Glucagon secretion

1- Blood glucose level: - glucagon secretion is increased by hypoglycemia and decreased by hyperglycemia. Its secretion is increased during starvation. Glucocorticoids are necessary for glucagon (permissive action) to exert its gluconeogenic effect during fasting or starvation.

2- Amino acids: increased concentrations after a high protein meal lead to increased glucagon secretion especially the glucogenic amino acids.

3- Exercise: will stimulate glucagon secretion due to:

a- The increased glucose utilization.

b- There is more autonomic nervous stimulation of pancreatic islets.

4-Sympathetic stimulation: to the pancreas produces beta adrenergic receptors stimulation (that are predomination in A cells) increased cAMP and increased glucagon secretion.

Stimulation of alpha adrenergic receptors inhibits secretion.

5- Vagal stimulation: increases glucagon secretion.

6- Stressful stimuli: increase glucagon via sympathetic stimuli.

7- GIT Hormones: CCK and Gastrin are increased by protein meal and increase glucagon secretion, while Secretin inhibits it.

8- Islet Cell Hormones: Somatostatin and insulin inhibit glucagon secretion.

somatostatin

Is secreted by the D cells of pancreatic islets and from the GIT.

1) All factors related to food ingestion stimulate its secretion.
   a- Increased blood glucose, A.A., and fatty acids.
   b- Increased GIT hormones as CCK.
2) It acts locally in a paracrine way to inhibit the pancreatic islets secretion of insulin, glucagon and pancreatic polypeptides.
3) Somatostatin secreted from the GIT, inhibits motility (stomach, duodenum, & gall bladder) secretion and absorption.

Regulation of Blood Glucose Level

Importance of Glucose Homeostasis

A constant blood glucose concentration is important because it is the only nutrient that can be used under normal conditions by the brain, retina and germinal epithelium of the gonads.

On the other hand flooding blood with glucose is not beneficial, because hyperglycemia has many harmful effects. **(look DM , effects of hyperglycemia).**

Control mechanisms and its components

A] Glucostatic Function of the Liver: -

a. During absorption (after a meal): The blood glucose rises to a high concentration and the rate of insulin secretion also rises. About 2/3 of the glucose absorbed from the gut is immediately stored in the liver in the form of glycogen.

b. In the postabsorptive period, during the following hours: the blood glucose level falls and the liver releases the glucose into the blood.

B] Hormonal Mechanism:

1. Insulin:
2. Glucagon:
3. Catecholamines:
4. Glucocorticoids:
5. Growth hormone:
6. Thyroid hormone:_

a. Both ***insulin*** and ***glucagon*** function as important feedback control systems for maintaining a normal blood glucose level:

- Hyperglycemia stimulates insulin secretion and insulin decreases the blood glucose level to normal
- Hypoglycemia stimulates glucagon secretion and glucagon increases the blood glucose back to normal

Under normal conditions, the insulin feedback mechanism is more important than glucagon.

Glucagon feedback mechanism is particularly valuable in starvation, during muscular exercise and in other stressful conditions.

b. **Severe hypoglycemia** stimulates the hypothalamus directly, which in turn stimulates the adrenal medulla to release ***epinephrine.*** Epinephrine in its turn increases glucose production from the liver through glycogenolysis, decreases glucose utilization by peripheral tissues, and it also causes a marked increase in the concentration of FFA in plasma to enhance the utilization of fat.

a. Hypoglycemia **prolonged** for hours and days (and during stress): leads to growth ***hormone*** and ***cortisol*** secretion.

Growth hormone produces:

- Glycogenolysis, lipolysis and ketogenesis.
- A decrease in the number of insulin receptors.
- A decrease in glucose utilization by peripheral tissues.

Cortisol produces:

- Gluconeogenesis, lipolysis and ketogenesis.
- A decrease in the affinity of insulin receptors to insulin.
- A decrease in glucose utilization by peripheral tissues.

Thyroid hormones produce:

-++ Glucose absorption from intestine

- Hepatic glycogen depletion

:***References***

-Ganong's Review of Medical Physiology.
-Guyton and Hall Textbook of Medical Physiology